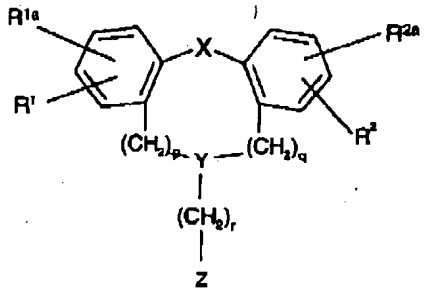
Attorney Docket No. 5776.204-US
Hansen et al.
Serial No. 09/872,127 Filed June 1, 2001
Via facsimile to: 571-273-0571

CLAIM LISTING

1. (Currently amended) A method for ~~treating a condition related to angiogenesis~~ **reducing angiogenesis or neovascularization**, said method comprising administering to a patient in need of such ~~treatement~~ **method** an effective amount of a compound having the general formula Ia



(Ia)

wherein R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, NR^7R^8, cyano, methylthio or $-SO_2NR^7R^8$ wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl ; and

Y is >N-CH_2- , >CH-CH_2- or >C=CH- wherein only the underscored atom participates in the ring system; or

Y is -CH_2N(-)CH_2-, -CH_2N(-)CH_2-, -(C=O)N(-)CH_2-, -CH_2N(-)(C=O)-, -CH_2CH(-)CH_2-, -CH_2CH(-)CH_2-, -CH_2C(-)=CH-, -CH=C(-)CH_2-, -OCH(-)CH_2-, -CH_2CH(-)O-, -SCH(-)CH_2-, -CH_2CH(-)S-, wherein only the underscored atom participates in the ring system; or

Y is >N-, >CH-, >N-(C=O)- or >C=C(R^8)-, wherein only the underscored atom participates in the ring system and R^8 is hydrogen or C_{1-6}-alkyl; or

Y is >CH-O- or >CH-S(O)$_y$ wherein y is 0, 1 or 2, or -N(R^8)- wherein R^8 is hydrogen or C_{1-6}-alkyl, and wherein only the underscored atom participates in the ring system; and

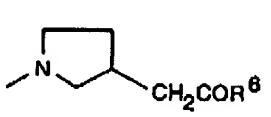
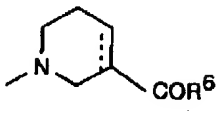
X is completion of an optional bond, ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH_2-, -CH_2-O-, -OCH_2O-, -CH_2OCH_2-, -S-CH_2-, -CH_2-S-, -(CH_2)N(R^8)-, -N(R^8)(CH_2)-, -N(CH_3)SO_2-, -SO_2N(CH_3)-, -CH(R^9)CH_2-, -CH_2CH(R^9)-, -(C=O)-

, -N(R^8)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and wherein R^9 is C_{1-6}-alkyl or phenyl; and

p and q independently are 0 or 1; and

r is 0,1, 2 , 3 or 4; and

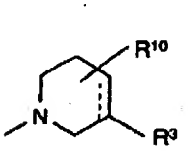
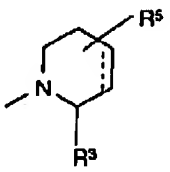
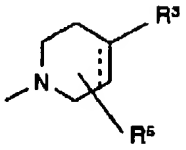
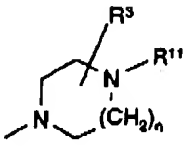
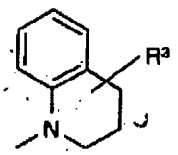
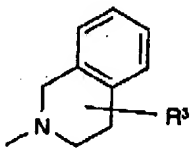
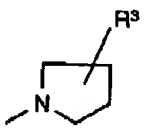
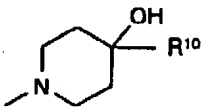
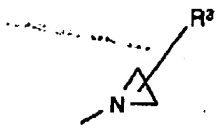
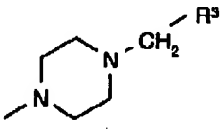
Z is selected from

wherein R^6 is OH or C_{1-6}-alkoxy; and

.... is optionally a single bond or a double bond; or

Z is selected from

wherein n is 1 or 2;

R^3 is $-(CH_2)_mOH$ or $-(CH_2)_sCOR^4$ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

R^4 is -OH, $-NH_2$, -NHOH or C_{1-6}-alkoxy; and

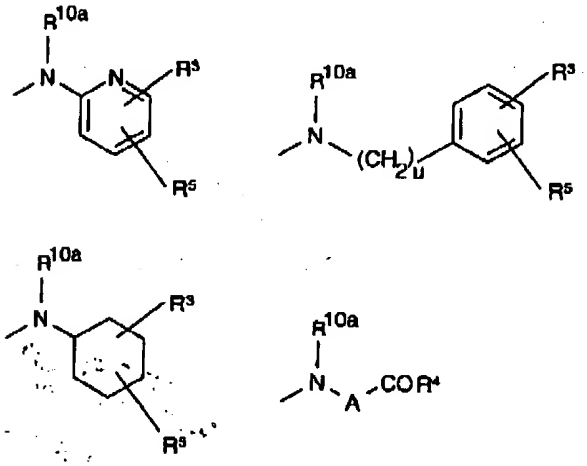
R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{10} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{11} is hydrogen or C_{1-6}-alkyl; and

.... is optionally a single bond or a double bond; or

Z is selected from



wherein u is 0 or 1;

R^3 is $-(CH_2)_mOH$ or $-(CH_2)_sCOR^4$ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

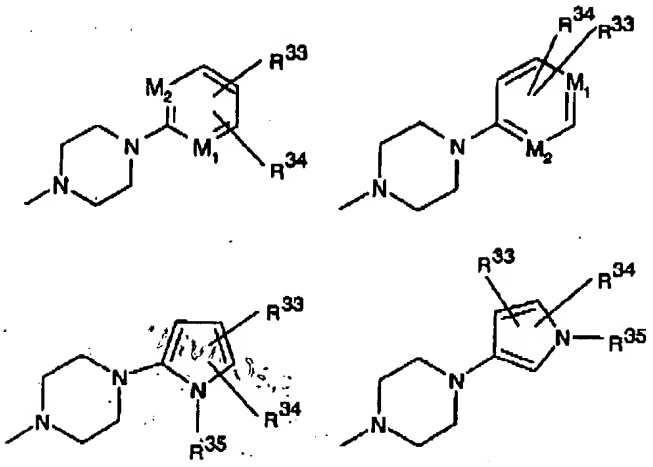
R^4 is -OH, $-NH_2$, -NHOH or C_{1-6}-alkoxy; and

R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{10a} is hydrogen or C_{1-6}-alkyl; and

A is C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene; or

Z is selected from



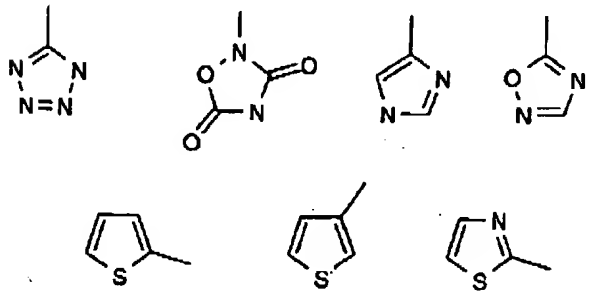
wherein M_1 and M_2 independently are C or N; and

R^{35} is hydrogen, C_{1-6}-alkyl, phenyl or benzyl; and

R^{33} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

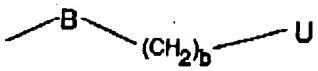
R^{34} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_wCOR^{31}$, $-(CH_2)_wOH$ or $-(CH_2)_wSO_2R^{31}$ wherein R^{31} is hydroxy, C_{1-6}-alkoxy or NHR^{32}, wherein R^{32} is hydrogen or C_{1-6}-alkyl, and w is 0, 1 or 2; or

R^{34} is selected from



; or

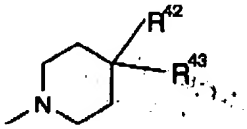
Z is



wherein b is 0, 1, 2, 3 or 4; and

B is -CH=CR^{49}-, -CR^{49}=CH-, -C≡C-, -(C=O)-, -(C=CH$_2$)-, -(CR^{49}R^{40})-, -CH(OR^{41})-, -CH(NHR^{41})-, phenylene, C$_{3-7}$-cycloalkylene or the completion of a bond, wherein R^{49} and R^{40} independently are hydrogen, C$_{1-6}$-unbranched alkyl, C$_{3-6}$-branched alkyl or C$_{3-7}$-cycloalkyl and wherein R^{41} is hydrogen or C$_{1-6}$-alkyl; and

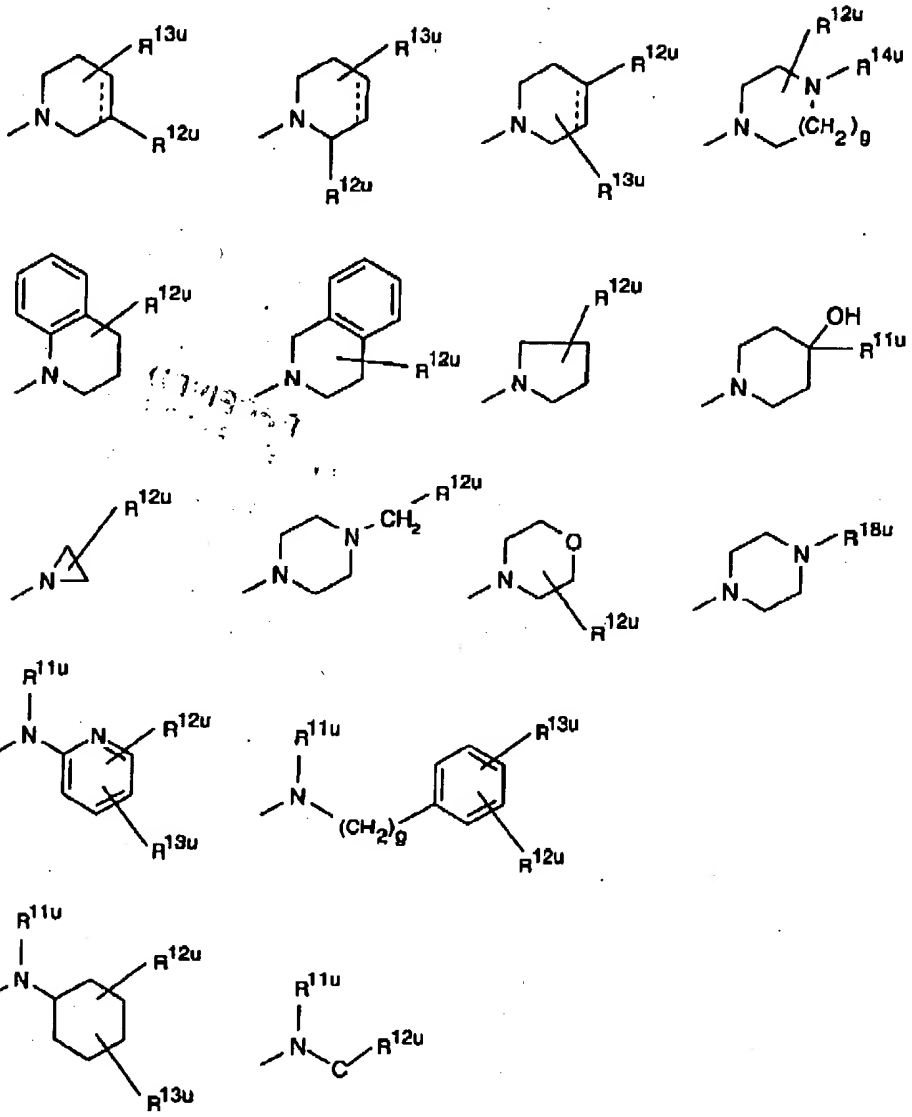
U is



wherein R^{42} is hydrogen, -(CH$_2$)$_c$OH or -(CH$_2$)$_d$COR^{47} wherein c is 0, 1, 2, 3, 4, 5 or 6 and d is 0 or 1 and wherein R^{47} is -OH, -NHR^{44} or C$_{1-6}$-alkoxy wherein R^{44} is hydrogen or C$_{1-6}$-alkyl; and

R^{43} is cyano, -NR^{45}R^{47}, -NR^{45}-V or -(CHR^{48})$_e$-V wherein R^{45} and R^{47} independently are hydrogen or C$_{1-6}$-alkyl and wherein e is 0, 1, 2, 3, 4, 5 or 6 and wherein R^{48} is hydrogen, halogen, cyano, trifluoromethyl, hydroxy, C$_{1-6}$-alkyl, C$_{1-6}$-alkoxy, -NR^{45}R^{47} or -COOH, and wherein V is C$_{3-8}$-cycloalkyl, aryl or heteroaryl, which rings may optionally be substituted with one or more halogen, cyano, trifluoromethyl, hydroxy, methylthio, C$_{1-6}$-alkyl or C$_{1-6}$-alkoxy; or

U is selected from



wherein g is 0, 1 or 2; and

R^{11u} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{12u} is $-(CH_2)_hOH$ or $-(CH_2)_jCOR^{17u}$ wherein h is 0, 1, 2, 3, 4, 5 or 6 and j is 0 or 1 and wherein R^{17u} is -OH, $-NHR^{20u}$ or C_{1-6}-alkoxy wherein R^{20u} is hydrogen or C_{1-6}-alkyl; and

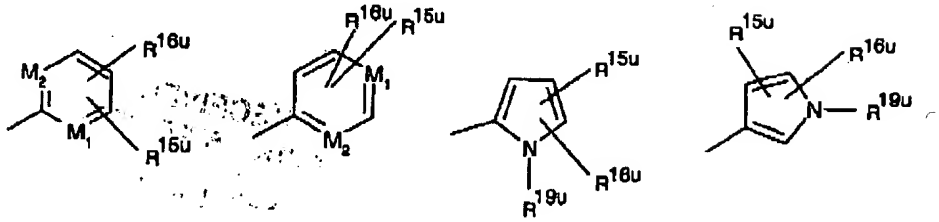
R^{13u} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{14u} is hydrogen or C_{1-6}-alkyl; and

C is C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene; and

---- is optionally a single bond or a double bond; and

R^{18u} is selected from



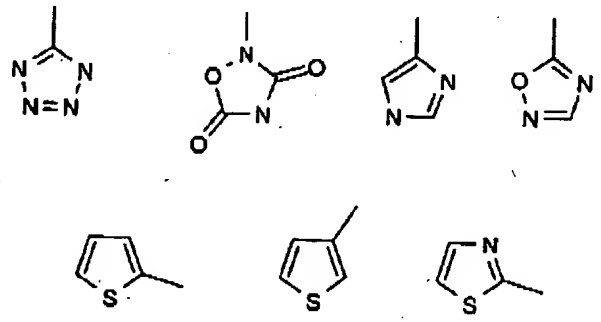
wherein M_1 and M_2 independently are C or N; and

R^{19u} is hydrogen, C_{1-6}-alkyl, phenyl or benzyl; and

R^{15u} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

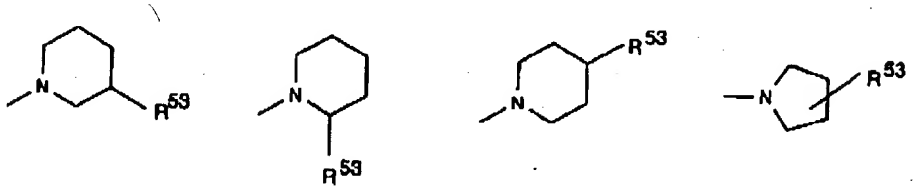
R^{16u} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_kCOR^{17u}$, $-(CH_2)_kOH$ or $-(CH_2)_kSO_2R^{17u}$ wherein k is 0, 1 or 2; or

R^{16u} is selected from



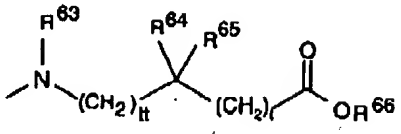
; or

Z is selected from



wherein R^{53} is $-(CH_2)_{pp}COOH$ wherein pp is 2, 3, 4, 5 or 6; or

Z is



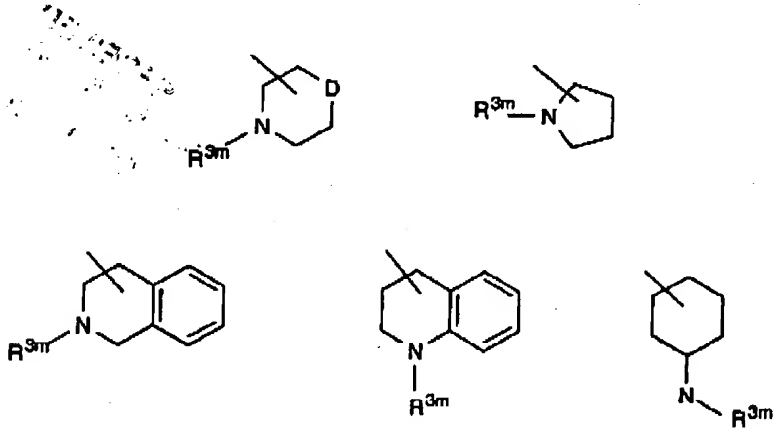
wherein tt and t independently are 0, 1 or 2; and

R^{63} is H, C_{1-6}-alkyl or optionally substituted benzyl;

R^{64} and R^{65} independently are H, C_{1-8}-alkyl, C_{3-7}-cycloalkyl, phenyl, thienyl, benzyl, or R^{64} and R^{65} together with the C-atom they are attached to form a 3 - 8 membered carbocyclic ring; and

R^{66} is H or C_{1-6}-alkyl; or

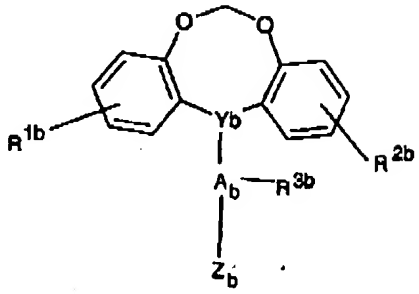
Z is selected from



wherein D is $-CH_2-$, -O-, -S- or $-N(R^7)-$ wherein R^7 is hydrogen or C_{1-6}-alkyl; and

R^{3m} is $-(CH_2)_{mm}OH$ or $-(CH_2)_{mp}COR^4$ wherein mm and mp are 1, 2, 3 or 4 and R^4 is OH, NH_2, NHOH or C_{1-6}-alkoxy; or

having the general formula Ib



(Ib)

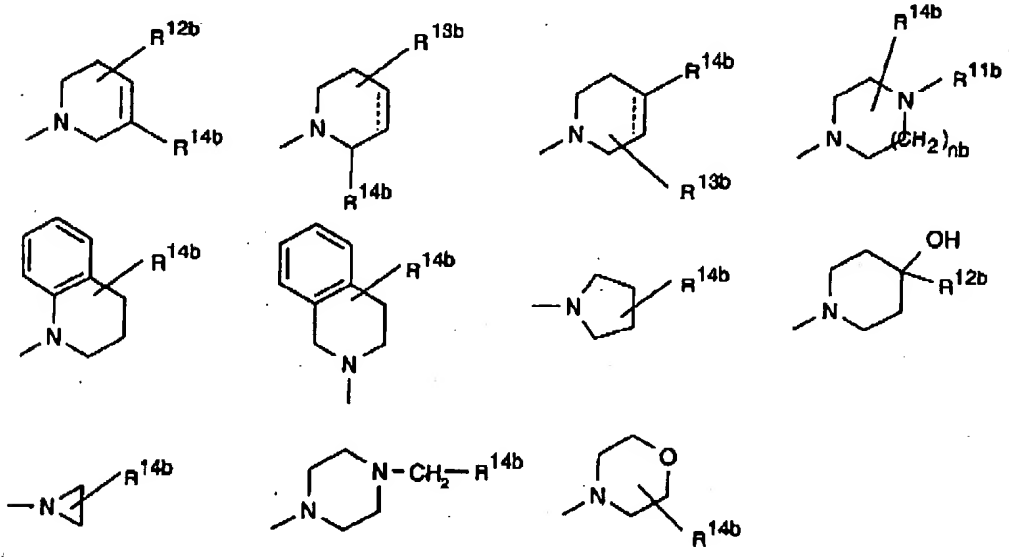
wherein R^{1b} and R^{2b} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

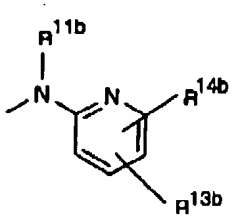
R^{3b} is hydrogen or C_{1-3}-alkyl; and

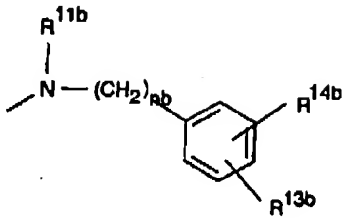
A_b is C_{1-3}-alkylene; and

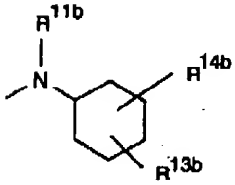
Y_b is >CH-CH_2-, >C=CH-, >CH-O-, >C=N-, >N-CH_2- wherein only the underscored atom participates in the ring system; and

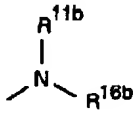
Z_b is selected from











wherein nb is 1 or 2; and

R^{11b} is hydrogen or C_{1-6}-alkyl; and

R^{12b} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or phenyl optionally substituted with halogen, trifluoro-methyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

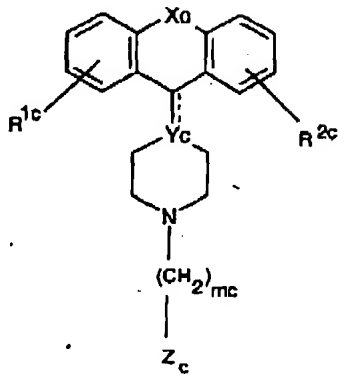
R^{13b} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{14b} is $-(CH_2)_{mb}OH$ or $-(CH_2)_{tb}COR^{15b}$ wherein mb is 0, 1, 2, 3, 4, 5 or 6 and tb is 0 or 1 and wherein R^{15b} is -OH, NH_2, -NHOH or C_{1-6}-alkoxy; and

R^{16b} is C_{1-6}-alkyl or $-B_b-COR^{15b}$, wherein B_b is C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene and R^{15b} is the same as above; and

... is optionally a single bond or a double bond; or

having the general formula Ic



(Ic)

wherein R^{1c} and R^{2c} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy;

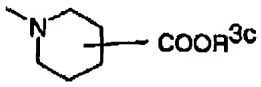
X_c is ortho-phenylene, -O-, -S-, $-C(R^{6c}R^{7c})-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^{8c})-(C=O)-$, $-(C=O)-N(R^{8c})-$, $-O-CH_2-$, $-CH_2-O-$, $-OCH_2O-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^{8c})-$, $-N(R^{8c})(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-CH(R^{10c})CH_2-$, $-CH_2CH(R^{10c})-$, -(C=O)-, $-N(R^{9c})-$ or -(S=O)- wherein R^{6c}, R^{7c}, R^{8c} and R^{9c} independently are hydrogen or C_{1-6}-alkyl, and wherein R^{10c} is C_{1-6}-alkyl or phenyl;

Y_c is C or N;

.... is optionally a single bond or a double bond, and .... is a single bond when Y_c is N;

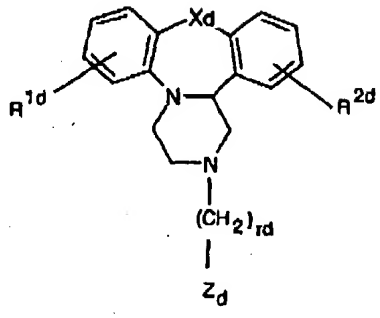
mc is 1, 2, 3, 4, 5 or 6; and

Z_c is $-COOR^{3c}$ or



wherein R^{3c} is H or C_{1-6}-alkyl; or

having the general formula Id



(Id)

wherein R^{1d} and R^{2d} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

X_d is -O-, -S- or -S(=O)-; and

rd is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 ; and

Z_d is selected from

wherein R^{3d} is $-(CH_2)_{md}OH$ or $-(CH_2)_{pd}COR^{4d}$ wherein md and pd independently are 0, 1, 2, 3 or 4 and R^{4d} is OH, NH_2, NHOH or C_{1-6}-alkoxy; or

a pharmaceutically acceptable salt of any of the foregoing.

2. (Currently amended) The method according to claim 1 wherein the **angiogenesis or neovascularization** ~~condition is related to~~ **reduction is for treatment of** cancer.

3. (Currently amended) The method according to claim 1 wherein the **angiogenesis or neovascularization is ocular** ~~condition is related to ocular neovascularization~~.

4. (Original) The method according to claim 1 wherein, in formula Ia,

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

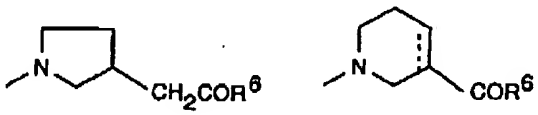
Y is >N-CH_2- , >CH-CH_2- or >C=CH- wherein only the underscored atom participates in the ring system; and

X is -O-, -S-, -$C(R^7R^8)$-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -$CH_2CH_2CH_2$-, -CH=CH-, -$N(R^8)$-(C=O)-, -O-CH_2-, -(C=O)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and

p and q are 0, and

r is 1, 2 or 3; and

Z is selected from



wherein R^6 is OH or C_{1-6}-alkoxy; and

.... is optionally a single bond or a double bond; and

a pharmaceutically acceptable salt of any of the foregoing.

5. (Original) The method according to claim 4 wherein the compound is selected from the group consisting of:

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid;

(R)-1-(3-(Fluoren-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(Thioxanthen-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-butyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10H-Phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10H-Phenoxazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-pyrrolidinacetic acid;

(R)-1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(2-Trifluoromethyl-10H-phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5-Oxo-10H-phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-10-Oxa-5-aza-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid;

(R)-1-(3-(6,7-Dihydro-5H-dibenzo[b,g]azocin-12-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-Methoxy-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10-Methyl-11-oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(9(H)-Oxo-10H-acridin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(2-(6,11-Dihydrodibenz[b,e]oxepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(Z)-(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(E)-(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Methoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride,

and a pharmaceutically acceptable salt of any of the foregoing.

6. (Cancelled)
7. (Cancelled)
8. (Cancelled)
9. (Cancelled)
10. (Cancelled)
11. (Cancelled)
12. (Cancelled)
13. (Cancelled)
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24. (Cancelled)
25. (Cancelled)
26. (Cancelled)
27. (Cancelled)
28. (Cancelled)
29. (Cancelled)
30. (Cancelled)
31. (Cancelled)
32. (Cancelled)

33. (Cancelled)

34. (Currently amended) The method according to claim 1 wherein the ~~pharmaceutical composition~~ **pharmaceutically acceptable salt** is in a form suitable for oral administration.

Attorney Docket No. 5776.204-US
Hansen et al.
Serial No. 09/872,127 Filed June 1, 2001
Via facsimile to: 571-273-0571

RESPONSE

The Examiner states in the Office Action Summary that claims numbered 1-34 are pending in the application, claims 6-33 are withdrawn from consideration, claims numbered 1, 2, 4, 5 and 34 are rejected, and claim number 3 is objected to.

(1) The Examiner has rejected claim number 1, 2, 4, 5 and 34 under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement. Specifically: the examiner states the specification, while being enabling for the specific cancer disclosed, does not reasonable provide enablement for the term "a condition related to angiogenesis" or "cancer".

Applicant has amended claims numbered 1, 2 and 3 to more clearly define the present invention. Applicant believes these amendments obviate the Examiner's rejection based on treatment of cancer and treatment of conditions related to angiogenesis.

Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

(2) The Examiner has rejected claim number 1, 2, 4, 5 and 34 under 35 U.S.C. §103(a) as being unpatentable over the Jørgensen et al. WO 96/31497.

Applicant has amended claims numbered 1, 2 and 3 to more clearly define the present invention. Applicant believes these amendments obviate the Examiner's rejection based on treatment of cancer.

Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

Applicant has amended claim 34 to correct antecedent basis.

In view of the above, Applicant respectfully submits all claims are in condition for allowance. *Applicant respectfully requests notification via an Advisory Action or telephone call if the Examiner deems the case is not in condition for allowance.*

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application. Applicant respectfully requests that

a timely Notice of Allowance be issued in this case.

Respectfully submitted,

Date: September 15, 2004

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Use the following customer number for all correspondence regarding this application.

23650
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